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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte KOJI YOSHINAGA, DAISUKE KAWASAKI, and YUTAKA EMORI[1]

Appeal 2014-007640
Application 12/632,182
Technology Center 1600

Before DONALD E. ADAMS, JOHN G. NEW, and DAVID COTTA, *Administrative Patent Judges.*

NEW, *Administrative Patent Judge*.

DECISION ON APPEAL

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[1]Appellants state the real party-in-interest is Zeria Pharmaceutical Co., Ltd. App. Br. 2.

SUMMARY

Appellants file this appeal under 35 U.S.C. § 134(a) from the Examiner's Final Rejection of claims 19–24, 27, 30, 31, 34, and 35, which stand rejected as unpatentable under U.S.C. § 103(a) as being obvious over the combination of Lee (US 6,537,988 B2, March 25, 2003) ("Lee") and Shinozaki et al. (US 6,239,131 B1, May 29, 2001) ("Shinozaki").

We have jurisdiction under 35 U.S.C. § 6(b).

We AFFIRM.

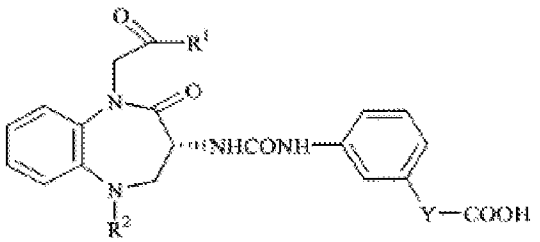
NATURE OF THE CLAIMED INVENTION

Appellants' invention is directed to pharmaceutical agent or an antitumor agent useful for the treatment and/or prevention of gastrointestinal cancer, leukemia, pituitary tumor, small cell lung cancer, thyroid cancer, and neuroastrocytoma. Abstr.

REPRESENTATIVE CLAIM

Claim 19 is representative of the claims on appeal and recites:

> Claim 19. A method for treating pancreatic cancer, the method comprising administering to a patient in need thereof an effective amount of ingredients (A) a 1,5-benzodiazepine derivative represented by the following formula (1):



(1)

> (wherein R^1 represents a C_{1-6} alkyl group; R^2 represents a phenyl group or a cyclohexyl group; and Y represents a single bond or a

> C_{1-4} alkylene group) or a pharmaceutically acceptable salt thereof, and (B) an antitumor agent.

App. Br. 15.

ISSUES AND ANALYSES

We agree with, and adopt, the Examiner's findings and conclusion that the appealed claims are obvious over the combined cited prior art references. We address the arguments raised on appeal by Appellants below.

Issue

Appellants argue the Examiner erred because the compounds taught by Lee and Shinozaki have such divergent structures that they would not have led one of ordinary skill to think of replacing the compounds of Lee with the claimed compound taught by Shinozaki with a reasonable expectation of achieving the synergistic effect taught by Lee. App. Br. 7.

Analysis

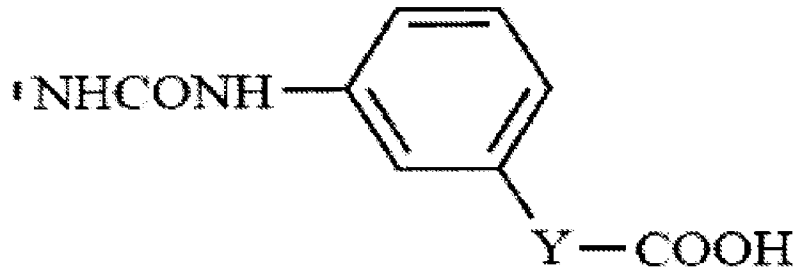
Appellants summarize the Examiner's position as relying upon Lee's teaching: (a) synergistic compositions that include the compounds of Lee's formula (1); (b) the synergistic compositions may include antitumor agents including 5-fluorouracil or gemcitabine; and (c) Lee teaches, *inter alia*, using the compositions to treat cancers of the pancreas. App. Br. 4 (citing Lee col. 2, ll. 15–55, col. 7, ll. 26–27, 34–35).

Appellants allege the Examiner then impermissibly relied upon hindsight analysis to combine these teachings with those of Shinozaki. App. Br. 4–5. Appellants point to the Examiner's finding that the compounds of

Shinozaki are of sufficient similarity to Lee's compounds, based on a similar core benzodiazepine structure, that a person of ordinary skill would replace the compounds of Lee with those of Shinozaki and in doing so "one would expect a reasonable expectation of success … would in fact also be effective for the treatment of pancreatic cancer." *Id.* at 5 (citing Final Act. 3–4). Appellants contend that this finding is erroneous because a person of ordinary skill in the art would not have been motivated to combine a different compound with the teachings of Lee teachings and reasonably expect the same or improved result, i.e., the required synergism. *Id.*

According to Appellants, Lee and Shinozaki are not similar enough in structure to be homologues in any formal sense, in that they are not positional isomers, adjacent homologues, etc. App. Br. 6. Appellants point to Lee's teaching a fused ring of a benzene and a heterocyclic seven-membered ring containing 2 nitrogen atoms, whereas Shinozaki also teaches a fused ring of a benzene and a heterocyclic seven-membered ring containing 2 nitrogen atoms but with the position of one of the nitrogen atoms being displaced by one position – i.e., the difference between the core structures being that Lee teaches a 2,5 benzodiazepine, whereas Shinozaki teaches a 1,5 benzodiazepine that encompasses Appellants' claimed compound. *Id.* Appellants also identify the following differences in the side chains between the compounds taught by Lee and Shinozaki:

> Using the labeling nomenclature of Lee in col. 2:
>
> > R 2 is required to be an optionally substituted lower alkyl or aralkyl (which preferably is an optionally substituted benzyl, col. 10, line 67). Yet in the compound of the present invention and Shinozaki, R 2 is =O.

> At the corresponding position where the following group is present in Shinozaki and the present invention, Lee has no group:
>
> 
>
>
> At the next position in Lee's compound corresponding to N-R_2 in the compound of present formula (I) and which is defined as a phenyl or cylcohexyl, Lee requires an optionally substituted imidazole linked via an alkyl group.
>
> Finally, Lee requires a substitutient at the R_1 position to be a Cl, Br, CN, optionally substituted phenyl or pyridyl yet there is no group at that position in the compound of formula (I) and that relied upon from Shinozaki.

App. Br. 6–7.

Appellants argue further that, given the differences between the benzodiazepine compounds taught by Lee and Shinozaki, a person of ordinary skill would not have found it obvious to try and substitute the compound of Shinozaki for those taught by Lee and have a reasonable expectation of success in achieving the synergistic results disclosed by Lee. App. Br. 6.

Appellants argue further that their claimed 1,5 benzodiazepine derivative does not exhibit a cytocidal effect when compared to conventional chemotherapeutic agents and therefore has a lower risk of serious side effects. App. Br. 10. Appellants assert that, when combined with another antitumor agent, their claimed compound yields a significant and unexpectedly improved antitumor effect. *Id.* (citing Spec. Ex. 2, 8).

The Examiner responds that Lee teaches a method of treating tumors, including pancreatic cancer, which comprises administering a benzodiazepine compound and 5-fluorouracil or alternatively gemcitabine, in which the combination exhibits a synergistic effect. Ans. 5 (citing Lee Table I; col. 17, ll. 60–65). The Examiner finds Lee does not teach Appellants' elected benzodiazepine derivative, however, Shinozaki teaches benzodiazepine compound that encompasses the scope of Appellants' claimed compound, and is also known to be used for the treatment of tumors. *Id.* The Examiner finds a person of ordinary skill in the art would reasonably expect success when substituting the benzodiazepine compound, of Shinozaki for that taught by Lee the treatment of pancreatic cancer. *Id.*

The Examiner finds one of ordinary skill would have been motivated to do so because it would have been reasonably expected that each of the compounds would exert the same, or substantially similar, anti-cancer activity without any appreciable loss of activity of the composition in achieving the disclosed therapeutic objective, absent factual evidence to the contrary. *Id.*

The Examiner finds that, contrary to Appellants' arguments, the base structures of Lee and Shinozaki are positional isomers. Ans. 6. The Examiner notes that compounds which are positional isomers or homologs are generally of sufficiently structural similarity that there is a presumed expectation that such compounds will possess similar properties. *Id.* (citing *In re Wilder*, 563 F.2d 457, 460 (C.C.P.A. 1977); MPEP § 2144.09(II). Moreover, the Examiner finds, the compounds taught by Lee and Shinozaki are each individually known to inhibit tumor growth. *Id.* Consequently, the Examiner concludes, those of ordinary skill would have had a reasonable

expectation that, as a class, benzodiazepine compounds share a similar mechanism of action and would therefore be therapeutically effective for the treatment of pancreatic cancer. *Id.*

We are not persuaded by Appellants arguments. Lee teaches the use of a benzodiazepine, in combination with an antitumor drug, produces a synergistic effect in the treatment of pancreatic cancer. *See* Lee, claims 1, 5, 8, col. 7, ll. 57–60; Ex. 6. Shinozaki similarly teaches a class of benzodiazepines, the basic structure of which is a positional isomer of the compounds taught by Lee, and which are also known to have antitumor activity. *See* Shinozaki, Abstr., col. ll. 19, 23–36. Appellants have not provided persuasive evidence to counter the expectation thatShinozaki's benzodiazepine compound would exhibit substantially similar anti-tumor activity to Lee's benzodiazepine compound when used in combination with another anti-tumor agent. We consequently agree with the Examiner that it would have been obvious to a person of ordinary skill in the art to substitute Shinozaki's benzodiazepine compound for Lee's benzodiazepine compound because Shinozaki' compound is a positional isomer of the same class, known to have antitumor activity. We also agree that a person of ordinary skill in the art would have a reasonable expectation of success in achieving a similar outcome. *See In re Kubin*, 561 F.3d 1351, 1361 (Fed. Cir. 2009).

Appellants argue that unexpected results rebut the Examiner's *prima facie* case of obviousness. App. Br. 9–13. We disagree at least because, for the reasons discussed above, the results achieved by the claimed method would not have been unexpected. Appellants contend that "when this [the Shinozaki compound] derivative is combined with another antitumor agent (ingredient (B) in Claim 19), a significant and unexpectedly improved

antitumor effect was obtained meaning that the dose can be reduced as well as attenuating the risks commonly associated with chemotherapeutic therapies." App. Br. 10. However, Appellants have not provided persuasive evidence that the claimed method provides unexpected results when compared to the closest prior art (Lee), which also shows a synergistic effect when combining a benzodiazepine and a chemotherapeutic agent. *See* Lee, Abstr. Instead, Appellants rely on data which compares the claimed methods to methods involving only monotherapy, which is not the closest prior art. *Id.* at 10–11. We consequently affirm the Examiner's rejection of the claims.

DECISION

The Examiner's rejection of claims 19–24, 27, 30, 31, 34, and–35 as unpatentable under 35 U.S.C. § 103(a) is affirmed.

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a)(1). *See* 37 C.F.R. § 1.136(a)(1)(iv).

AFFIRMED